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(54) Title: A METHOD OF TREATMENT OF MANIA AND BIPOLAR DISORDER

(57) Abstract

The present invention is a novel therapeutic use of gabapentin, its derivatives, and the pharmaceutical salts thereof. The compounds are useful in the treatment of mania in all its various forms whether acute or chronic, single or recurrent, and whether or not it is associated with depression. The invention further includes the preventative treatment of bipolar disorder.

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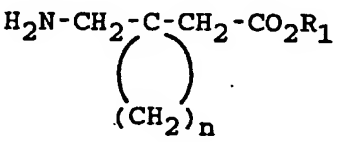
A METHOD OF TREATMENT OF MANIA AND BIPOLAR DISORDER

BACKGROUND OF THE INVENTION

United States Patent Numbers 4,024,175 and 4,087,544, which are incorporated herein by reference, teach cyclic amino acids of formula



wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6 and the pharmaceutically acceptable salts thereof.

The compounds disclosed in the above United States patents are useful for the therapy of certain cerebral diseases, for example, they can be used for the treatment of certain forms of epilepsy, faintness attacks, hypokinesia, and cranial traumas. Additionally, they bring about an improvement of cerebral functions and thus are useful in treating geriatric patients. Particularly valuable is 1-(aminomethyl)-cyclohexane-acetic acid (gabapentin).

United States Patent Number 5,084,479 teaches the compounds of the above formula for therapeutic use in neurodegenerative disorders such as Alzheimer's, Huntington's, Parkinson's, and Amyotrophic Lateral Sclerosis. It also teaches the use of the compounds in the treatment of acute brain injury such as stroke, head trauma, and asphyxia.

United States Patent Number 5,025,035 teaches the use of the compounds of the above formula for depression.

United States Patent Application Serial Number 08/281285 teaches the use of the compounds ofthe above formula to treat anxiety and/or panic disorders.

There is no disclosure in the above references to make obvious the present invention of novel uses of the compounds of United States Patent Number 4,024,175 to treat mania and/or bipolar disorder.

SUMMARY OF THE INVENTION

The present invention relates to novel therapeutic uses of a known compound, gabapentin, its derivatives, and pharmaceutically acceptable salts. The invention concerns a method for treating the symptoms of mania in a human in need of such treatment. This method includes, but is not limited to the treatment of mania in all its various forms whether acute or chronic, single or recurrent episode, and associated with depression or not. The invention further includes the preventive treatment of bipolar disorder in persons predisposed to this disorder.

Episodes of acute mania are characterized by elevated or irritable mood, disturbed sleep, grandiosity, increased motor activity, pressured thinking, distractibility and poor concentration, impaired judgement, and sometimes psychotic symptoms. The irritability can lead to outbursts of angry or aggressive behavior. Often the episodes are preceded by a period of disturbed sleep. The distractibility makes the patient move endlessly from one activity to another often to the detriment of their physical, occupational, and social well-being. The impact of

these behaviors is further aggravated by the lapses of judgement and poor decision-making that is characteristic of this illness.

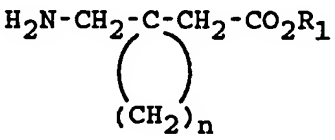
Episodes of mania occur in patients who suffer from bipolar disorder which is an illness characterized by alternating cycles of depression and mania. This disorder is distinct from the more common form of depression, called Major Depressive Disorder, in which patients only experience recurrent episodes of depression but no mania. Bipolar disorder can be diagnosed by the clinical evaluation of patients using the criteria specified in the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association. In this nomenclature system, bipolar disorder is subsumed under the broader class of Mood Disorders and is clearly distinguished from the Anxiety Disorders and from Organic Mental Disorders.

In studies of epilepsy, gabapentin has been noted to reduce anger and irritability, enhance concentration, and improve decision-making abilities. These effects will be beneficial in the symptomatic treatment of patients suffering from mania who exhibit irritability, distractibility, and poor judgement. This is a novel use for gabapentin which would not be obvious to a medical practitioner of ordinary skill.

In one study gabapentin has also been found to enhance delta-wave (deep) sleep. This effect will be beneficial in acute mania and will also lead to reducing the risk for onset of a new episode of mania in a predisposed individual. Thus, the prophylactic use of gabapentin for bipolar disorder is also taught.

DETAILED DESCRIPTION

The present invention relates to novel methods of treating mania and/or bipolar disorder in a mammal in need of such treatment. The treatment comprises administering in unit dosage form an effective amount of a compound of formula



wherein R_1 is hydrogen or a lower alkyl and n is 4, 5, or 6 or a pharmaceutically acceptable salt thereof. The term lower alkyl includes straight or branched chain alkyl groups of up to 8 carbon atoms.

Preferred compounds of Formula I above include but are not limited to 1-aminomethyl-1-cyclohexane-acetic acid, ethyl 1-aminomethyl-1-cyclohexane-acetate, 1-aminomethyl-1-cycloheptane-acetic, acid 1-aminomethyl-1-cyclopentane-acetic acid, methyl 1-aminomethyl-1-cyclohexane-acetate, n-butyl 1-aminomethyl-1-cyclohexane-acetate, methyl 1-aminomethyl-1-cycloheptane-acetate, n-butyl 1-aminomethyl-1-cycloheptane-acetate, toluene sulfonate, 1-aminomethyl-1-cyclopentane-acetate, benzene-sulfonate, and n-butyl 1-aminomethyl-1-cyclopentane-acetate.

The most preferred compound is 1-aminomethyl-cyclohexane acetic acid (gabapentin).

Pharmaceutical compositions of the compound of the present invention or its salts are produced by formulating the active compound in dosage unit form with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, pills, powders, aqueous and nonaqueous oral solutions and

suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses. Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch, cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations. The compositions of the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents.

The percentage of the active ingredients in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredient is present.

Routes of administration of the subject compound or its salts are oral or parenteral. For example, a useful intravenous dose is between 5 and 50 mg and a useful oral dosage is between 20 and 200 mg. The

dosage is within the dosing range used in epilepsy treatment or as would be with the needs of the patient as described by the physician.

A unit dosage form of the instant invention may also comprise other compounds useful in the therapy of neurodegenerative diseases.

The advantages of using the compounds of Formula I, especially gabapentin, in the instant invention include the relatively nontoxic nature of the compound, the ease of preparation, the fact that the compound is well-tolerated, and the ease of IV administration of the drug. Further, the drug is not metabolized in the body.

The subjects as used herein are mammals, including humans.

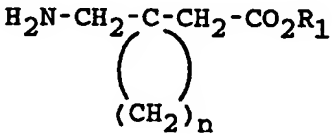
The usefulness of compounds of Formula I above and the salts thereof as agents for mania in all its various forms and in the preventative treatment of bipolar disorder is demonstrated in its effects on the mental functions of patients. These effects were observed during epilepsy clinical trial. See Table 1 below wherein the effects beneficial to patients with bipolar disorder are presented.

TABLE 1

Patient No.	Effect
1	More relaxed
2	More socially responsive, better concentration
3	More sharp cognitively, more relaxed. Decreased confusion, increased comprehension
4	Less nervous energy, more serene
5	More relaxed
6	Less insomnia
7	Thinking is clearer
8	Psychic improvement, more present, more relaxed
9	Able to think more clearly
10	More clear than before
11	More relaxed
12	More relaxed and somehow better
13	Feels better, has not been so impulsive
14	Alertness and speech have improved
15	More alert and able to concentrate better
16	More clear headed, memory has improved

CLAIMS

1. A method for treating the symptoms of mania in a mammal in need of said treatment which comprises administering a therapeutically effective amount of a compound of formula



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or a pharmaceutically acceptable salt thereof wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6 in unit dosage form.

2. A method according to Claim 1 wherein the mania is acute.

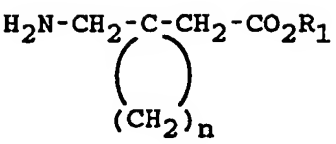
3. A method according to Claim 1 wherein the mania is chronic.

4. A method according to Claim 1 wherein the mania is a single episode.

5. A method according to Claim 1 wherein the mania is recurring.

6. A method according to Claim 1 wherein gabapentin is administered.

7. A method for treating and/or preventing bipolar disorder in a mammal in need of said treatment which comprises administering a therapeutically effective amount of a compound of formula



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or a pharmaceutically acceptable salt thereof wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6 in unit dosage form.

8. A method according to Claim 7 wherein the compound administered is gabapentin.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/05898

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 024 175 (SATZINGER GERHARD ET AL) 17 May 1977 cited in the application	1-8
A	EP,A,0 446 570 (WARNER LAMBERT CO) 18 September 1991 cited in the application	1-8
A	US,A,5 025 035 (WALLACE JAN D) 18 June 1991 cited in the application	1-8
A	WO,A,91 19493 (US ARMY) 26 December 1991 see claim 2	1-8
A	US,A,4 355 044 (HELLER BERNARDO) 19 October 1982	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 1996	- 2. 08. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I ıational application No.
PCT/US96/05898

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-8 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int. nal Application No
PCT/US 96/05898

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4024175	17-05-77	DE-A-	2460891	01-07-76
		AT-B-	340892	10-01-78
		AU-B-	8774175	23-06-77
		BE-A-	836835	18-06-76
		CA-A-	1052811	17-04-79
		CH-A-	612665	15-08-79
		CH-A-	612666	15-08-79
		CH-A-	612664	15-08-79
		DE-A-	2543821	14-04-77
		FR-A,B	2294697	16-07-76
		GB-A-	1465229	23-02-77
		JP-C-	941538	20-02-79
		JP-A-	51088940	04-08-76
		JP-B-	53024064	18-07-78
		LU-A-	74058	20-07-76
		NL-A-	7514900	23-06-76
		SE-B-	423385	03-05-82
		SE-A-	7514442	22-06-76
		US-A-	4087544	02-05-78
EP-A-0446570	18-09-91	US-A-	5084479	28-01-92
		AT-T-	125701	15-08-95
		DE-D-	69111642	07-09-95
		DE-T-	69111642	25-01-96
		JP-A-	4210915	03-08-92
US-A-5025035	18-06-91	CA-A-	2092416	13-04-92
		EP-A-	0552240	28-07-93
		JP-T-	6502148	10-03-94
		WO-A-	9206686	30-04-92
WO-A-9119493	26-12-91	US-A-	5086072	04-02-92
		AU-B-	651125	14-07-94
		AU-B-	8208491	07-01-92
		CA-A-	2085135	19-12-91
		EP-A-	0533832	31-03-93
		JP-T-	6501454	17-02-94
US-A-4355044	19-10-82	US-A-	4431670	14-02-84